thymic importation regulatory processes, (2) a significant defect in regeneration of the BM progenitor pool capable of thymic seeding, and (3) intrathymic niches remain unsaturated for extended periods.

Using the same CCR7/CCR9 DKO animals this group used previously to demonstrate their importance for steady-state thymic importation of progenitors, Zlotoff and colleagues found that after lethal irradiation and HSCT there is a brief window where the regular dependence of thymic entry on CCR9 and CCR7 is broken. In assessing the kinetics of this uncoupling they found that while there was reduced reconstitution from CCR7/CCR9 DKO compared with wild-type animals, there was still significant contribution from CCR7/CCR9 DKO cells up to 3 weeks after transplantation, after which their relative contribution declined considerably. Interestingly, the importance of PSGL-1 in this process of thymic importation was maintained even after irradiation. Zlotoff et al then go on to show that the BM-resident $Lin^{-}ckit^{+}Flt3^{+}$ fraction, which contains most T-lineage progenitors after transplantation, was significantly depleted for at least 4 weeks after transplantation. This finding indicates that increasing the supply of progenitors could considerably enhance thymic reconstitution. Indeed this was the case, and thymic reconstitution was significantly increased in a dose-dependent fashion.

These findings suggest that even despite the uncoupling of CCR7 and CCR9 from the process of thymic seeding, deficiency in the supply of progenitors from the BM leads to unsaturated thymic niches for at least 10 weeks after transplantation, ultimately causing delayed reconstitution. Moreover, taken together with the prolonged availability of intrathymic niches, the uncoupling of the processes regularly used in steady-state thymopoiesis could provide further evidence at the molecular level of the regulation of thymic "gates" and the periodic entry of precursor T cells postulated by Goldschneider and colleagues[11]—a process that is likely disrupted after irradiation. It will be of considerable interest to identify the regulating factors at play in the irradiated setting and, critically, how these can be manipulated to enhance thymic reconstitution after HSCT.

These studies by Zlotoff et al represent an important advance in furthering our understanding of the processes underpinning thymic seeding, particularly in the context of the clinically relevant situation of immune reconstitution after HSCT. Their findings highlight that in attempting strategies to enhance thymic reconstitution we must not only focus on the thymus and its ability to support T-cell development, but also on the supply of BM-resident progenitors that can seed the thymus. These crucial insights will not only aid in developing strategies to enhance thymic reconstitution using precursor T cells,[12] but also offer an important target for manipulation of thymic importation of progenitors for achieving tolerance to solid organ transplants and generating efficient and effective antitumor responses.

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● ● ● TRANSPLANTATION

Comment on Miller et al, page 1971

X-ALD: centralize care in an international network

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In this issue of *Blood*, Miller et al describe the efficacy of hematopoietic cell transplantation (HCT) in 60 patients with childhood cerebral adreno-leucodystrophy (ALD).[1] To further improve the outcomes of cellular treatment options in this very rare disease, there is need for coordination of care and a well-functioning international clinical and research network.

After the first report from Aubourg in 1990[2] and a 2004 international report from Peters et al (n = 126 of whom only 94 with complete dataset were analyzed),[3] the data from Miller et al once again demonstrate efficacy of transplantation for otherwise rapidly fatal childhood neurodegenerative disease. The outcomes from this recent (2003-2009) single-center cohort are encouraging, with an overall survival rate of ~ 80%, with ~ 90% survival for those who receive a transplant when minimally affected (absent neurologic disease or Loes score < 10). In line with previous reports,[2-4] predictors for poor survival/disease progression after HCT were high Loes scores (> 10) or having neurologic dysfunction before HCT. Miller and colleagues speculate that better supportive care in the past decade and better patient selection are the main causes of improved survival rates in this recent cohort. Several centers, most notably the University of Minnesota, have been leaders in advancing the care of patients with inherited metabolic diseases (IMDs). In

addition, Miller et al present the long-term (neurologic) outcomes of HCT and the impact of adjuvant treatment with NAC (N-acetyl-L-cysteine) on survival, and they speculate on how to improve outcomes further. These are all very important issues to move the field forward.

Further improvement of the outcomes (survival and neurologic) of this very rare, devastating disease (which should also apply for other rare IMDs) can only happen when we as a transplant community: (1) centralize and coordinate the cellular therapies (such as HCT and gene-therapy) for these rare diseases and (2) tighten the international collaboration through a well-functioning international network.

The most important argument for these recommendations is the rarity of the disease. With the exception of the University of Minnesota, there are no other centers in the world transplanting these numbers of X-linked ALD (X-ALD) patients (60 in 6 years). In the study by Peters et al, only 126s patients were included from 43 centers between 1989 and 1999.[3] This demonstrates that it is very difficult to perform single-center studies (for studying novel therapies), gain experience in clinical care, provide multidisciplinary follow-up (because most patients continue to have residual disease burden), and recognize typical disease-specific, post-HCT complications. For X-ALD, future topics of interest include:

1. How can we improve survival rates and neurologic outcome?

2. Can toxicity be further reduced using nonmyeloablative conditioning regimens, which may result in better survival and neurologic outcome?

3. Does mixed-chimerism, which may be a result from reduced-intensity conditioning, influence the long-term results as it does in other IMDs (eg, Hurler disease)?[5] If it does, it may have implications for gene-therapy trials as well.

4. Can we optimize the outcomes with adjuvant therapies, such as NAC, which was shown by Miller et al in a previous report to impact the survival in neurologically affected patients before HCT?[1,6] As previously mentioned, there is need for further study of the effect of adjuvant therapies, such as NAC, to further improve outcomes.

5. Patients (and parents) may profit from well-organized, dedicated, disease-specific, multidisciplinary teams. As early diagnosis and early transplantation influence outcome, early recognition of certain problems, which may be part of residual disease burden, is of importance to prevent more severe morbidities. This can be done best by experienced teams in specialized centers.

For X-ALD (which may also apply to other IMDs), nationwide, regional, or state-centralized care may improve outcomes after HCT. It would substantially increase the experience of the multidisciplinary teams caring for these rare diseases, increase data collection for international studies, and promote uniform treatment protocols or guidelines. These centers should be organized as clinical and research networks. In The Netherlands there has been 1 national referral center (UMC Utrecht) for HCT in IMDs since 2004. Within a multidisciplinary team the indication for HCT is made and after transplantation there is a standardized, multidisciplinary follow-up program for these patients. This has definitely impacted the process of care for this vulnerable patient group. In the past decade, international collaboration, such as the introduction of transplantation guidelines for IMD within the European Group for Blood and Marrow Transplantation, has resulted in better outcomes (higher survival and lower morbidity rates). For example, the survival rate of HCT in Hurler syndrome increased from 50% to > 90%.[7] And currently, an international long-term follow-up study, including the majority of the European- and North American–transplanted Hurler syndrome patients, is in its analyses phase.

We have to build on these collaborations to continue to improve treatment in X-ALD and other IMDs. Greater international collaboration will lead to better outcomes in this interesting and challenging field.

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● ● ● VASCULAR BIOLOGY

Comment on Cheng et al, page 1998

Channeling the homocysteine chapel

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Hyperhomocysteinemia (HHcy), a potent risk factor for cardiovascular disease, is associated with impaired endothelium-dependent vasodilation. In this issue of *Blood*, Cheng et al report that severe HHcy causes oxidation and tyrosine nitration of small and intermediate conductance Ca^{2+}-activated potassium channels, resulting in impaired endothelium-derived hyperpolarizing factor (EDHF)–mediated relaxation of resistance arterioles.[1]

When functioning normally, the endothelium regulates vasomotor tone and local hemostasis by releasing vasodilator substances (nitric oxide, prostacyclin, or EDHF mediators) and vasoconstrictor substances (endothelin-1, angiotensin II, thromboxane A_2, or free radicals).[2] Linking HHcy to specific potassium channel dysfunction and impaired EDHF-mediated relaxation points to new therapeutic targets with potentially broad relevance in HHcy-related atherothrombotic disease (see figure).

Loss of endothelial responsiveness, an important aspect of overall endothelial dysfunction, is an early event in the pathogenesis of atherosclerosis, and maintaining endothelial